

No evidence of disease activity in people with multiple sclerosis (NEDA in PwMS)

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The advances in the management of people with multiple sclerosis (pwMS) in past 12 years have been incomparable. It is now possible to prevent the relentless course of active MS much better and aim at better outcomes for our patients. Are better outcomes achieved with “**no evidence of disease activity**” or **NEDA**? What is NEDA and does it matter?

We discuss NEDA now, because we can and do actively look for relapses or sub-clinical MRI signs of MS inflammation in order to **escalate** the treatment efficacy. Even 10 years ago, most pwMS with clinical relapses under treatment with one interferon-beta 1 (IFNb) would be offered another IFNb or glatiramer acetate (GA).

Natalizumab, fingolimod, dimethyl fumarate, teriflunomide, alemtuzumab, cladribine and ocrelizumab have joined several formulations of IFNb and GA in the options of disease modifying drugs (DMD) used to reduce the inflammatory relapses and disability progression.

The first licensed drug for people with progressive MS has just been licensed.

A larger choice of DMD makes NEDA possible, but treatment decisions more difficult: informed risk-benefit assessments based on data from clinical and drug trials and medical history are necessary. It is now possible to do a tentative personalised medicine in pwMS.

The initial step of identifying people with active MS to start DMD is now earlier, as earlier treatment has better outcomes (1): time is brain. The diagnostic criteria developed in/for trials are based in clinical measures of relapses (neurological symptoms clinical worsening for over

24 hours without another explanation) or disability progression MRI, and oligoclonal bands (OCB) in cerebrospinal fluid (CSF).

In opposition to the usual strategy of escalation of DMD, the use of alemtuzumab as a first line DMD defines a strategy of induction, where a high efficacy drug is used earlier. After two infusions twelve months apart, more treatment is given only when there is evidence of disease activity.

For pwMS treated with IFN β , there is evidence that two or more lesions in the brain magnetic resonance imaging (MRI) scan are indicative of treatment failure and a need to escalate sooner (2).

Apart from clinical measures, NEDA relies on MRI and CSF as biomarkers. Currently, MRI is an accepted tool for the diagnosis and identification of MS activity: gadolinium-enhancing T1-weighted lesions, new or enlarging T2/FLAIR lesions represent inflammatory MS activity, whereas measures of atrophy are used in clinical trials as an outcome measure. The presence of OCB in the CSF (exclusively, or in larger number than in the serum) defines the dissemination in time for the diagnostic criteria and allows earlier diagnosis and treatment. Biomarkers of MS activity reached a new target when the end-products of axonal degeneration - neurofilament light (NFL) chains - started to be reliably measured in the CSF: high levels indicate damage associated with acute inflammation and neurodegeneration (3).

The difficulties in the use of NEDA in clinical practice encompass different areas: regular MRI scans of the brain are expected to be done with similar acquisitions and slice thicknesses and be reviewed by experienced neuroradiologists who have time to evaluate number of lesions or with imaging softwares that facilitate the comparison. The safety of repetitive Gadolinium use is questioned and the random timing has limited use to identify enhancement in areas that are “clinically silent”. Measurements of brain atrophy are not usually done in clinical practice as variability of the measures is still debated. Further, excess atrophy represents an end-stage brain damage that early DMD use intends to avoid.

On the other hand, CSF NFL levels are earlier measurements of axonal damage, but require a lumbar puncture and access to the small number of laboratories that perform the test. Serum measurements of NFL are a great hope but the methods that can detect low NFL levels are still not validated in clinical practice.

In summary, MS neurologists aim to have pwMS with NEDA, as this indicates that pwMS are well treated (4). How to assess the activity of MS and safety of DMD switches in order to have long-term benefits is still under debate.

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